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Remodeling the Ischemic Stroke Immuno-Microenvironment via Microglial Phenotypic Switching

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Abstract: Ischemic stroke triggers a complex cascade of sterile inflammation that critically influences neurological outcomes. While reperfusion therapies remain the standard of care, their efficacy is often undermined by secondary brain injury driven by the pro-inflammatory polarization of microglia. As the central orchestrators of the central nervous system (CNS) immuno-microenvironment, microglia exhibit dynamic plasticity, shifting between the neurotoxic M1 phenotype and the neuroprotective M2 phenotype. The pathological transition from an M2-dominant state to a sustained M1 state perpetuates neuronal death and blood-brain barrier disruption. This review comprehensively elucidates the spatiotemporal dynamics of microglial polarization and the molecular mechanisms governing this switch, with a particular focus on key signaling pathways. Furthermore, we summarize emerging therapeutic strategies, including pharmacological modulation, stem cell-derived exosomes, and stimuli-responsive nanomedicine, aimed at precisely remodeling the immuno-microenvironment. We conclude that promoting the M1-to-M2 phenotypic switch represents a promising therapeutic avenue to mitigate reperfusion injury and enhance long-term functional recovery.

Keywords: Ischemic stroke; Microglia; Neuroinflammation; Phenotypic switching; Immuno-microenvironment; Immunometabolism

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1. Introduction

Ischemic stroke remains a devastating global health crisis, standing as a leading cause of mortality and long-term disability worldwide. Currently, the restoration of cerebral blood flow through recombinant tissue plasminogen activator (rt-PA) thrombolysis or mechanical thrombectomy represents the gold standard for clinical treatment [1,2]. However, the efficacy of these recanalization therapies is severely constrained by narrow therapeutic time windows and the potential risk of hemorrhagic transformation. Crucially, successful recanalization does not guarantee tissue survival; on the contrary, the rapid restoration of blood supply often paradoxically exacerbates tissue damage and dysfunction, a phenomenon known as cerebral ischemia-reperfusion injury (IRI) [3]. This suggests that targeting vascular recanalization alone is insufficient, and there is an urgent need for neuroprotective adjuncts that can mitigate the secondary injury cascade following the initial ischemic insult.

Accumulating evidence underscores that stroke is not merely a hemodynamic event but a complex thrombo-inflammatory pathology. Following the onset of ischemia, the deprivation of glucose and oxygen leads to neuronal death

and the release of damage-associated molecular patterns (DAMPs), such as HMGB1 and ATP. These danger signals trigger a robust sterile immune response, transforming the ischemic brain into a highly dynamic "immuno-microenvironment." This microenvironment is characterized by the breakdown of the blood-brain barrier (BBB), the accumulation of inflammatory mediators, and the complex interplay between resident glial cells and infiltrating peripheral immune cells. Among these components, the regulation of neuroinflammation has emerged as a critical determinant of stroke outcome, dictating whether the brain tissue progresses towards necrosis or recovery [4,5].

Microglia, the resident macrophages and primary immune sentinels of the central nervous system (CNS), act as the "central orchestrators" of this immuno-microenvironment. Under physiological conditions, microglia maintain CNS homeostasis by monitoring synaptic activity and clearing metabolic debris. However, they are highly plastic and sensitive to environmental perturbations. In the context of ischemic stroke, microglia are the first responders, rapidly activating and undergoing morphological and functional transformations. Their ubiquity and rapid response capability make them the most pivotal therapeutic target for modulating the post-stroke inflammatory landscape [6].

The functional role of microglia in ischemic stroke is often described as a "double-edged sword," contingent upon their polarization phenotypes. Historically, activated microglia have been categorized into two distinct states: the "classically activated" M1 phenotype and the "alternatively activated" M2 phenotype. The M1 phenotype is pro-inflammatory, releasing cytotoxic cytokines (*e.g.*, TNF-α, IL-1β) and reactive oxygen species (ROS) that exacerbate blood-brain barrier disruption and neuronal apoptosis. Conversely, the M2 phenotype exerts neuroprotective effects by phagocytosing cellular debris and secreting anti-inflammatory cytokines (*e.g.*, IL-10) and neurotrophic factors (*e.g.*, BDNF). In the pathology of stroke, a transient M2-like response is often overwhelmed by a sustained and aggressive M1-like polarization, leading to chronic inflammation and poor functional recovery. Therefore, shifting the microglial phenotype from the destructive M1 state to the reparative M2 state, rather than broadly suppressing the immune system, represents a promising strategy to remodel the immuno-microenvironment [7].

In this review, we comprehensively summarize the spatiotemporal dynamics of microglial polarization and the molecular mechanisms governing this phenotypic switching. We specifically focus on key signaling pathways, including the TLR4/NF-κB and JAK/STAT axes, which serve as molecular switches for polarization. Furthermore, we highlight emerging therapeutic interventions, ranging from pharmacological modulation and natural compounds to advanced nanomedicine and stem cell-derived exosome therapies. By elucidating the mechanisms of microglial phenotypic switching, this review aims to provide new insights into remodeling the immuno-microenvironment for the treatment of ischemic stroke (**Figure 1**).

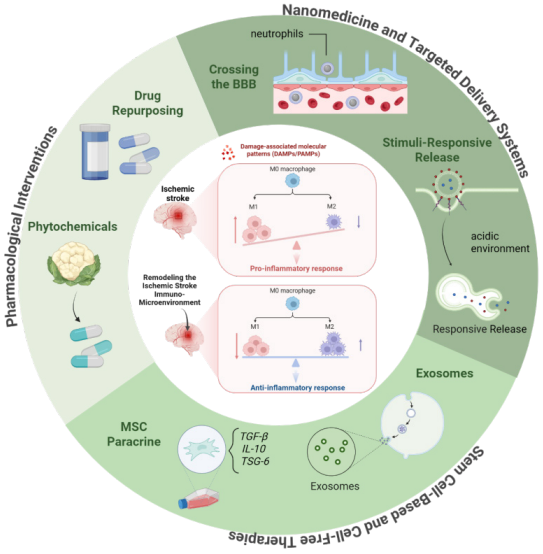

Figure 1. Schematic representation of therapeutic strategies targeting microglial phenotypic switching to remodel the ischemic stroke immuno-microenvironment.

2. Dynamic shifts of microglial phenotypes

2.1. The dichotomy of polarization

Historically, based on the macrophage classification system, activated microglia have been categorized into two opposing functional states: the "classically activated" M1 phenotype and the "alternatively activated" M2 phenotype. Although this binary classification is increasingly recognized as a simplification of a complex biological reality, it remains a valuable conceptual framework for understanding the duality of neuroinflammation.

2.1.1. The M1 phenotype

Upon stimulation by DAMPs (*e.g.*, HMGB1, ATP) or pro-inflammatory mediators (*e.g.*, IFN-γ), resting microglia polarize towards the M1 state. These cells are characterized by the upregulation of surface markers such as CD16, CD32, CD86, and major histocompatibility complex II (MHC-II). Functionally, M1 microglia act as the "soldiers" of the immune system. They secrete high levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12) and cytotoxic mediators like nitric oxide (NO) generated by inducible nitric oxide synthase (iNOS) and ROS [8]. While this response is intended to combat pathogens, in the sterile environment of ischemic stroke, the excessive accumulation of M1-derived toxins exacerbates neuronal apoptosis, compromises BBB integrity, and expands the infarct volume [9,10].

2.1.2. The M2 phenotype

In contrast, the M2 phenotype represents a reparative state induced by cytokines such as IL-4, IL-13, and IL-10. M2 microglia are identified by the expression of CD206 (mannose receptor), Arg-1 (Arginase-1), and Ym1. The M2 population is functionally diverse and can be further subclassified into M2a (tissue repair), M2b (immunoregulation), and M2c (debris clearance). Collectively, M2 microglia secrete anti-inflammatory cytokines (IL-10, TGF-β) and potent neurotrophic factors and vascular endothelial growth factor (VEGF). These cells play a pivotal role in resolving inflammation, phagocytosing necrotic debris, and promoting angiogenesis and neurogenesis in the recovery phase [11,12].

2.2. Spatiotemporal evolution

The polarization of microglia is not a fixed state but follows a distinct temporal trajectory during the progression of ischemic stroke. The imbalance in this temporal evolution, the failure to sustain the M2 phenotype, is a key driver of secondary brain injury.

2.2.1. Acute phase (Hours to 3 Days)

In the hyper-acute phase immediately following ischemia, microglia are rapidly activated. Accumulating preclinical evidence suggests that resident microglia initially adopt an M2-dominant phenotype, limiting the spread of the lesion and scavenging early cellular debris. This early M2 response is likely a physiological attempt to restore homeostasis [13,14].

2.2.2. Subacute phase (3 Days to 7 Days)

As the ischemic cascade advances, the massive accumulation of necrotic debris and danger signals overwhelms the regulatory capacity of the microenvironment. This leads to a decisive phenotypic shift where the M2 population declines, and the M1 phenotype becomes predominant. This period coincides with the peak of the "cytokine storm," where M1 microglia recruit circulating neutrophils and monocytes, further amplifying the inflammatory response [13–15].

2.2.3. Chronic phase (Weeks to Months)

In the chronic phase of stroke, while the acute inflammation subsides, M1-like microglia often remain chronically activated at the lesion border. This persistent, low-grade inflammation sustains oxidative stress and promotes the formation of a dense glial scar, which acts as a physical and chemical barrier to axonal regeneration. The inability of the brain to revert to or maintain an M2-resolving phenotype impedes long-term functional recovery [13,15].

2.3. Spatial heterogeneity and transcriptomic complexity

Beyond temporal dynamics, microglial phenotypes exhibit significant spatial heterogeneity, particularly distinguishing the infarct core from the ischemic penumbra.

2.3.1. Core vs. penumbra

In the infarct core, where blood flow is severely restricted, microglia are rapidly depleted. In contrast, the penumbra, the metabolically compromised but salvageable tissue surrounding the core, is the primary site of microglial activation and self-renewal. Here, pro-inflammatory ($CD16^+$) and anti-inflammatory ($Arg1^+$) microglial phenotypes coexist, with their competing functions determining tissue fate through a "tug-of-war". Notably, HDAC3 selectively drives proliferation of pro-inflammatory microglia without affecting anti-inflammatory subsets, suggesting that targeting this pathway specifically within the penumbra represents a promising therapeutic strategy [16,17].

2.3.2. Beyond the binary

It is crucial to acknowledge that recent advances in single-cell RNA sequencing (scRNA-seq) have challenged the strict M1/M2 dichotomy. Transcriptomic analysis reveals that stroke-associated microglia do not simply fall into two distinct clusters but present a multidimensional spectrum of activation states. For instance, specific subsets such as "Disease-Associated Microglia" (DAM) have been identified, which express unique lipid-metabolism genes involved in debris clearance. While the M1/M2 classification remains useful for describing functional outcomes, researchers must recognize this complexity, suggesting that future therapies may need to target specific sub-populations rather than broadly modulating inflammation [18,19].

3. Molecular mechanisms underlying polarization

The phenotypic switching of microglia is not a stochastic event but a tightly regulated process governed by an intricate network of intracellular signaling pathways, transcriptional regulators, and metabolic checkpoints.

3.1. Pro-inflammatory signaling axes

The rapid induction of the M1 phenotype following ischemia is primarily orchestrated by pattern recognition receptors (PRRs) and their downstream cascades. Among these, the TLR4/NF-κB axis and the NLRP3 inflammasome represent the most critical pathways.

3.1.1. The TLR4/NF-κB canonical pathway

Toll-like receptor 4 (TLR4) serves as a pivotal gatekeeper in the sterile immune response. In the ischemic brain, necrotic neurons release high-mobility group box 1 (HMGB1), heat shock proteins (HSPs), which function as DAMPs [20]. Upon binding to these ligands, TLR4 undergoes homodimerization and recruits the cytosolic adaptor protein myeloid differentiation primary response 88 (MyD88) [21].

This recruitment triggers a phosphorylation cascade involving IL-1 receptor-associated kinases (IRAK1 and IRAK4) and TNF receptor-associated factor 6 (TRAF6). TRAF6 subsequently activates the transforming growth factor-β-activated kinase 1 (TAK1), which phosphorylates the IκB kinase (IKK) complex. The activated IKK complex targets the inhibitor of nuclear factor-κB (IκBα) for phosphorylation and ubiquitination, leading to its proteasomal degradation. This liberation allows the NF-κB p65/p50 heterodimer to translocate from the cytoplasm to the nucleus. Once nuclear, NF-κB binds to specific consensus sequences on DNA, driving the transcription of pro-inflammatory genes [21]. This pathway not only initiates the cytokine storm but also upregulates the expression of NLRP3, setting the stage for inflammasome activation [22].

3.1.2. The NLRP3 inflammasome

While NF-κB provides the "priming" signal by upregulating NLRP3 and pro-IL-1β expression, a secondary activation signal in the ischemic microenvironment triggers NLRP3 oligomerization [23].

Upon activation, the NLRP3 sensor protein oligomerizes and recruits the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD) and pro-Caspase-1. This assembly leads to the autocatalytic cleavage of pro-Caspase-1 into active Caspase-1. Active Caspase-1 then processes the inactive precursors pro-IL-1β and pro-IL-18 into their mature, biologically active forms. Furthermore, Caspase-1 cleaves Gasdermin D (GSDMD), the N-terminal fragment of which forms pores in the plasma membrane, causing pyroptosis—a highly inflammatory form of programmed cell death that releases massive amounts of cytokines into the extracellular space, further propagating the M1 response [24].

3.2. Anti-inflammatory signaling pathways

Counteracting the pro-inflammatory drive, several signaling pathways are responsible for inducing and maintaining the M2 phenotype. Enhancing these pathways is a key strategy for "immunomodulation."

3.2.1. The JAK/STAT signaling pathway

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway plays a dual role in microglial polarization, with specific STAT isoforms dictating divergent outcomes. While STAT1 is generally associated with IFN-γ-induced M1 polarization, STAT3 and STAT6 are critical drivers of the M2 phenotype [25].

For instance, the binding of IL-4 or IL-13 to their respective receptors activates JAK1 and JAK3, which phosphorylate cytosolic STAT6. Phosphorylated STAT6 dimerizes and translocates to the nucleus, where it induces the transcription of M2 signature genes, such as Arg1 (Arginase-1), Mrc1 (CD206). Similarly, IL-10 exerts its anti-inflammatory effects primarily through the STAT3 signaling axis. The activation of STAT3 suppresses the expression of pro-inflammatory mediators and promotes the release of neurotrophic factors. The balance between STAT1 and STAT3/6 activation is often regarded as a molecular "switch" determining microglial fate [26].

3.2.2. The Nrf2/HO-1 antioxidant axis

Oxidative stress is a potent trigger for inflammation. The nuclear factor erythroid 2-related factor 2 (Nrf2) is the master regulator of the cellular antioxidant defense. Under basal conditions, Nrf2 is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (Keap1), which targets it for ubiquitination [27].

In response to oxidative stress, Nrf2 dissociates from its cytoplasmic repressor Keap1, translocates to the nucleus, and binds to Antioxidant Response Elements (AREs) to promote the expression of antioxidant enzymes, notably heme oxygenase-1 (HO-1). HO-1 catalyzes heme degradation into biliverdin, iron, and carbon monoxide, thereby augmenting cellular antioxidant capacity [28]. Critically, Nrf2 activation concurrently suppresses the NLRP3 inflammasome and NF-κB signaling, leading to reduced expression of pro-inflammatory mediators including IL-1β, IL-6, and TNF-α. This dual antioxidant and anti-inflammatory effect is abrogated by pharmacological Nrf2 inhibition, confirming that Nrf2 acts as a master regulator coupling oxidative stress defense with inflammatory response modulation [27,28].

4. Therapeutic strategies targeting phenotypic switching

Given the central role of microglial polarization in stroke pathology, shifting the microglial phenotype from the destructive M1 state to the reparative M2 state represents a pivotal therapeutic goal. Unlike broad-spectrum anti-inflammatory agents that may hinder the beneficial clearance of debris, "immunomodulatory" strategies aim to fine-tune the immune response, restoring the balance of the microenvironment.

4.1. Pharmacological interventions: repurposing and natural compounds

Pharmacological modulation remains the most accessible approach. This category includes the repurposing of FDA-approved drugs and the exploration of bioactive natural compounds (phytochemicals).

4.1.1. Drug repurposing

(1) Metformin: Widely used for diabetes, metformin has demonstrated robust neuroprotective effects [29]. It promotes M2 polarization primarily by activating AMPK (AMP-activated protein kinase). Activated AMPK inhibits the NF-κB pathway and suppresses the NLRP3 inflammasome [30]. Furthermore, metformin improves mitochondrial function, supporting the metabolic shift required for the M2 phenotype [31].

(2) Fingolimod (FTY720): An immunomodulator approved for multiple sclerosis. While primarily known for sequestering lymphocytes, fingolimod also acts directly on microglial S1P receptors (S1PR) [32], biasing them towards an anti-inflammatory state via the STAT3 pathway [33].

4.1.2. Phytochemicals

(1) Curcumin: Derived from turmeric, curcumin is a potent PPAR-γ agonist. It inhibits TLR4 signaling and promotes M2 polarization. However, its clinical application is limited by poor bioavailability, necessitating novel formulation strategies [34,35].

(2) Resveratrol: A polyphenol found in grapes, resveratrol activates SIRT1 (Sirtuin 1). SIRT1 deacetylates the p65 subunit of NF-κB, inhibiting its transcriptional activity, thereby suppressing the M1 response and promoting antioxidant defenses via the Nrf2 axis [36,37].

4.2. Stem cell-based and cell-free therapies

Stem cell therapy has evolved from the concept of "cell replacement" to "paracrine modulation." Specifically, Mesenchymal Stem Cells (MSCs) are the most promising candidates due to their potent immunomodulatory properties.

4.2.1. MSC paracrine mechanisms

Transplanted MSCs secrete a "secretome" rich in soluble factors like TGF-β, IL-10, and TSG-6. These factors interact with host microglia, suppressing M1 activation and fostering an M2-dominant microenvironment. Importantly, MSCs can "sense" the inflammatory environment and adjust their secretion profile accordingly [38,39].

4.2.2. Exosomes

Direct stem cell transplantation faces challenges such as low survival rates, immune rejection, and tumorigenesis risks. Consequently, focus has shifted to Exosomes (small extracellular vesicles, 30-150 nm) derived from MSCs [40,41].

Exosomes are stable, have low immunogenicity, and can cross the BBB more efficiently than whole cells. They function as carriers of biological information, primarily miRNAs. For example, MSC-derived exosomes enriched with miR-124 (a microglia-specific miRNA) or miR-223 have been shown to target molecules in the NF-κB pathway, effectively "silencing" pro-inflammatory genes and inducing M2 polarization. This "cell-free therapy" represents a safer and more controllable alternative for clinical translation [42].

4.3. Nanomedicine and targeted delivery systems

A major hurdle in treating CNS disorders is the BBB, which prevents nearly 98% of small-molecule drugs from reaching the brain[43,44]. Furthermore, systemic administration of immunomodulators can cause off-target immunosuppression. Nanomedicine offers precise solutions to these challenges.

4.3.1. Crossing the BBB

Nanoparticles (NPs) such as liposomes, dendrimers, and polymeric micelles can be engineered to penetrate the BBB. Strategies include receptor-mediated transcytosis (*e.g.*, coating NPs with transferrin or lactoferrin) or "hitchhiking" on circulating immune cells (*e.g.*, neutrophils) [45–47] that naturally migrate to the ischemic brain.

4.3.2. Stimuli-Responsive release

The ischemic microenvironment has unique characteristics: acidosis (low pH) and high ROS levels. "Smart" ROS-responsive nanoparticles can be designed to degrade and release their drug cargo only when they encounter the high-ROS environment of the M1-polarized zone [48–50]. This spatiotemporal control maximizes therapeutic efficacy while minimizing systemic toxicity.

5. Conclusion

In summary, the phenotypic switching of microglia acts as a central fulcrum in the pathophysiology of ischemic stroke. The pathological transition from a reparative M2 phenotype to a detrimental M1 state is driven by a complex interplay between signaling pathways (*e.g.*, TLR4/NF-κB, JAK/STAT) and immunometabolic reprogramming. Therefore, therapeutic strategies capable of "remodeling" this microenvironment offer a superior approach compared to broad immunosuppression.

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Disclosure statement

The author declares no conflict of interest

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